REMARKS

Claims 1-16 are currently pending. Claims 4-13 are withdrawn from consideration as a result of the Restriction Requirement dated August 31, 2006.

Claim Rejections -- 35 U.S.C. § 112, second paragraph

Applicants respectfully traverse the rejections of claims 1-3 as allegedly being unclear. A person skilled in the art would readily understand that claim 1 is drawn to a crystalline form of fexofenadine hydrochloride characterized by the power X-ray diffraction (PXRD) peaks recited in the claim. The person would also readily understand that claim 2 is drawn to the crystalline form of fexofenadine hydrochloride of claim 1 having a PXRD pattern substantially as depicted in Fig. 6. Claim 3 is clear to the person as directed to fexofenadine hydrochloride Form IX as disclosed in the specification. The Office Action asserts that "PXRD although is useful in delineating crystalline structure," PXRD "does not offer reliable information on the chemical identity of a material." Applicants submit that the chemical nature of the products according to claims 1-3 is clear to the person skilled in the art. The products according to claims 1-3 has the chemical nature of being a crystalline form of fexofenadine hydrochloride having at least the characteristic PXRD peaks recited in claim 1. The chemical name of fexofenadine is well known in the art as 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]-α,α-dimethylbenzeneacetic acid (see page 1, lines 6-7, the instant specification). Fexofenadine has a chemical structure as depicted in formula (I) in page 1, line 10, of the instant specification. Coupled with the PXRD peaks recited in claim 1, the person skilled in the art would readily know the chemical nature of the products according to claims 1-3.

The Office Action cites "Bernstein p.372" as allegedly indicating that "identical PXRD would be obtained for different chemical material were the crystalline structures are identical." Actually, p. 372 of Bernstein, J., *Polymorphism in Molecular Crystals* (Clarendon Press, 2002) is silent on different chemical materials having identical PXRD. Instead Fig. 8.4 in page 272 of the book authored by Bernstein indicates that two pigments differing only in having two methyl groups instead of two chloro atoms as

substituents have been reported to have very similar powder X-ray diffraction patterns. However, the showing in Fig. 8.4 of Bernstein, as allegedly caused by the methyl versus chloro substitution, would not be a problem for the instant claims because the instant claims are directed to the crystalline form of one compound, *i.e.*, fexofenadine hydrochloride, or 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]-α,α-dimethylbenzeneacetic acid hydrochloride, having at least the PXRD peaks recited in claim 1. There are not different substituents.

The Office Action also cites p. 118 of the book authored by Bernstein for the proposition that it "is well recognized in the art that powdered X-ray diffraction can be drastically different from its single crystal X-ray. Applicants note that Fig. 4.21 in page 118 of Bernstein shows that preferred orientation of the crystals of sulfphathiazole Form III has been shown to suppress a number of the peaks in the experimental powder X-ray diffraction pattern as compared with the peaks in the expected powder X-ray diffraction pattern calculated from the single crystal structure. But Bernstein emphasizes that Fig. 4.21 was a "dramatic example of preferred orientation" (Bernstein, J., *Polymorphism in Molecular Crystals*, p. 117, first full paragraph, Clarendon Press, 2002). However, there is no evidence that the powder X-ray diffraction patterns disclosed in the instant patent application were collected improperly so that there was preferred orientation induced artifacts. Just like any other equipment, the operation of an X-ray powder diffractometer has to be conducted by someone with proper training and care in order to obtain reliable experimental data. Bernstein understands this because, despite the showing of the suppressive effect of preferred orientation on sulphathiazole in Fig. 4.21, Bernstein does not discount the usefulness of the X-ray powder diffraction technique. In fact, despite the "dramatic example of preferred orientation" shown in Fig. 4.21, Bernstein concludes that "X-ray powder diffraction is probably the most definitive method for identifying polymorphs and distinguishing among them" (*Polymorphism in Molecular Crystals*, p. 112, second full paragraph, second to the last sentence, Clarendon Press, 2002). In the instant case, there is no evidence or indication that the Scintag X-ray powder diffractometer was not used properly to collect the powder X-ray diffraction data disclosed in the instant application. Thus, there is no evidence or indication that the powder X-ray diffraction patterns disclosed in the specification and the PXRD peaks

recited in claim 1 are not reliable to be used to characterize the claimed crystalline fexofenadine hydrochloride.

The x-ray pattern of a crystalline substance can be considered as a "fingerprint" with each crystalline substance having, within limits, a unique diffraction pattern. Dean, *Analytical Chemistry Handbook*, p. 10.24 (1995). "The existence of polymorphs is best established by x-ray crystallographic examination." Byrn, S.R. *Solid-State Chemistry of Drugs*, p. 79 (Academic Press 1982).

> X-ray powder diffraction is perhaps the "gold standard" for the qualitative determination of crystallinity. Not only can the presence of a crystalline phase be confirmed, but since each polymorph produces a unique diffraction pattern, the question of which polymorph crystallized can be addressed.

Brittain, H.G., *Polymorphism in Pharmaceutical Solids* pp. 398-99 (Marcel Dekkler 1999).

As disclosed in page 12, lines 11-16, fexofenadine hydrochloride Form IX is a solvate of cyclohexane or MTBE.

Withdrawal of the indefiniteness rejections is requested.

Claim Rejection -- 35 U.S.C. § 112, first paragraph

Applicants respectfully traverse the rejection of claim 15 under 35 U.S.C. § 112, first paragraph allegedly for nonenablement. The Office Action asserts that it is conventional expectation that polymorphic forms of crystals are metastable which will convert to the thermodynamically stable form upon formulation. Applicants disagree that polymorphic forms of crystals are generally metastable. There is no evidence or suggestion that the crystalline fexofenadine hydrochloride Form IX-MTBE solvate or Form IX-cyclohexane solvate is metastable. The scope of claim 15 is not broad.

Withdrawal of the lack of enablement rejection is requested.

Claim Rejections -- 35 U.S.C. § 102(b)

I. Applicants respectfully traverse the rejections of claims 1 and 2 as allegedly anticipated by Ortyl '872 (US 5,738,872).

The Office Action asserts that every PXRD peak recited in claim 1 and 2 are found in Table 19 of Ortyl '872. Applicants disagree. Ortyl '872 discloses the PXRD peaks in the unit of d-space, Angstrom (Table 19, column 30). Since the PXRD peaks recited in claim 1 and the PXRD pattern depicted in Fig. 6 are given in the unit of degrees 2θ, for the convenience of the Examiner, applicants have converted the PXRD peaks of Table 19 from d-space, Angstrom, to degrees 2θ using Bragg equation. The result of the conversion is shown in the table below.

PXRD Peaks of Ortyl Fexofenadine HCl Form II (Table 19)

d-space (Angstroms)	Degrees 2θ	I/I_o (%)
11.41	7.8	20
7.98	11.1	20
7.83	11.3	45
6.58	13.5	45
6.42	13.8	60
5.66	15.7	20
5.52	16.1	45
5.39	16.5	30
5.23	17.0	65
5.14	17.3	45
4.86	18.3	65
4.72	18.8	100
4.45	20.0	65
4.40	20.2	45
4.32	20.6	45
4.18	21.3	45
4.06	21.9	65
4.02	22.1	55
3.85	23.1	25
3.79	23.5	75
3.74	23.8	95

3.61	24.7	80
3.56	25.0	25
3.47	25.7	65
3.41	26.1	20
2.74	32.7	20

A comparison of the PXRD peaks of the crystalline fexofenadine HCl disclosed in Table 19 of Ortyl '872 with the PXRD peaks recited in claim 1 and depicted in Fig. 6, it is apparent that the crystalline fexofenadine HCl disclosed in Table 19 of Ortyl '872 is different from the crystalline fexofenadine HCl of claims 1 and 2 because the crystalline fexofenadine HCl disclosed in Table 19 of Ortyl '872 lacks at least the following recited PXRD peaks: 4.7, 9.3, 19.4, 19.6 and 21.6 degrees 2θ.

Withdrawal of the anticipatory rejections of claims 1 and 2 over Ortyl '872 is requested.

II. Applicants respectfully traverse the rejection of claim 16 as allegedly anticipated by Carr (US 4,254,129).

The Office Action alleges that claim 16 was anticipated by Examples 2-3 of Carr. Applicants disagree because Examples 2 and 3 of Carr merely disclose fexofenadine hydrochloride recrystallized from butanone and methanol-butanone (Example 2) or from methanol-butanone (Example 3). Carr does not disclose the crystalline fexofenadine hydrochloride having the chacteristic PXRD peaks recited in claim 1. Thus, Carr does not teach a method of using the crystalline fexofenadine hydrochloride having the chacteristic PXRD peaks recited in claim 1 to inhibit the binding between an H1 receptor and histamine in a mammal.

Withdrawal of the anticipatory rejection of claim 16 over Carr is requested.

Claim Rejections -- 35 U.S.C. § 103(a)

Applicants respectfully traverse the rejections of claims 1-3 and 14-16 as obvious under 35 U.S.C. § 103(a) over Ortyl '872 (US 5,738,872) in view of Evans, US Pharmacopoeia and Brittain.

Ortyl '872 differs from claims 1-3 and 14-16 at least in not disclosing the crystalline fexofenadine hydrochloride with the characteristic PXRD peaks recited in claim 1 or substantially as depicted in Fig. 6. The four crystalline forms of fexofenadine hydrochloride disclosed by Ortyl '872 are different from the crystalline fexonfenadine hydrochloride according to claims 1-3 and the Form IX-MTBE solvate or Form IX-cyclohexane solvate in the pharmaceutical composition of claim 14, the unit dosage of claim 15 and the pharmaceutical composition administered in the method of claim 16. Evans, US Pharmacopoeia and Brittain fail to cure the deficiencies of Ortyl '872 because the preparation and formation of crystalline forms of an organic compound are unpredictable. There is no reasonable prediction of (a) how many crystalline forms an organic compound will have, (b) whether a specific crystalline form of the organic compound will exist, and (c) how to prepare a specific crystalline form of the organic compound. Evans, US Pharmacopoeia and Brittain do not provide any such prediction, and do not even suggest that the crystalline fexofenadine hydrochloride characterized by at least the PXRD peaks recited in claim 1 exists and do not provide any teaching of preparing the the crystalline fexofenadine hydrochloride characterized by at least the PXRD peaks recited in claim 1 with a reasonable expectation of success. Thus, claims 1-3 and 14-16 would not have been obvious over the prior art relied upon by the Office Action.

Withdrawal of the obviousness rejections of claims 1-3 and 14-16 is requested.

The Examiner is urged to call the undersigned if there remains any minor issues that can be resolved with a telephone interview.

In the event that the filing of this paper is deemed not timely, applicants petition for an appropriate extension of time. The petition fee and any other fee that may be required in relation to this paper can be charged to Deposit Account No. 11-0600.

Respectfully Submitted,
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